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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 05/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/883,119	ELLINGTON ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9-14,128 and 137* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9-14,128 and 137* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Office Action mailed 4-20-05, at page 3, included claims 7 and 8 as being rejected under 35 USC 103(a). This statement of rejection was improper since Applicants canceled claims 7-8 in the amendment filed 10-15-04.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The prior Office Action improperly stated that claims 1-14, 128 and 138 were rejected, the action should have stated that claims 1-14, 128 and 137 were rejected by the examiner in the Office Action mailed 4-20-04.

4. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Response to Amendment

5. The amendment to the claims filed 10-15-2004 and reproduced on pages 16-17 of the Appeal Brief filed 12-15-04 does not comply with 37 CFR 1.121(c)(2) because the term "between" in line 2 of claims 3 and 4 (as set forth in the claim amendment filed 1-23-04) was removed from these claims. However there are no markings in the amendment filed 10-15-2004 to indicate that this change had occurred. As per 37 CFR § 1.121(c)(2) The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. Amendments to the claims filed on or after July 30, 2003 must comply with 37 CFR 1.121(c).

Response to Arguments

6. Applicant's arguments, see Appeal Brief, filed 12-15-04, with respect to claims 1-14, 128 and 137 have been fully considered and are persuasive. The rejection of claims 1-14, 128 and 137 has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made under 35 USC § 103(a) over George et al. in view of Breaker et al. US Patent No. 6,630,306 B1 and King (4-12-2000). Additionally, new grounds for rejection of claim 6 under 35 USC 112, 1st paragraph are set forth below.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-5, 9-14, 128 and 137 are rejected under 35 U.S.C. 103(a) as being unpatentable over George et al. (US 5,834,186) in view of Breaker et al. (US Patent No. 6,630,306) and King (4-12-2000).

9. George et al. disclose regulatable polynucleotides having a catalytic domain that is linked to a ligand binding sequence, placing the activity of the catalytic domain under the control of that ligand and requiring the presence of the ligand for activation or inactivation (col. 3, lines 1-5). The polynucleotides are constructed in which one portion is capable of binding a ligand and the other portion is a catalytic nucleic acid. The ligands may be small organic or inorganic molecules, macromolecules such as proteins, nucleic acid molecules, a polysaccharide or sugars (see col. 5, lines 37-40; and col. 7, lines 24-44).

Based upon the schematic representation of the ligand binding regulatable ribozymes of George et al. in Figures 1c-1d, it appears that the ribozyme sequence is partially double stranded and the ligand portion binding of the ribozyme is single stranded.

Figure 2 of George et al. describe a mechanism by which the protein effector may be encoded by the target RNA, or may be provided exogenously. Example 3 of the specification as filed provides inducible transcription or translation vectors comprising regulatable ribozymes.

Although George et al. teaches that catalytic DNA molecules with ligand binding behavior may also be found using the disclosed methods (see col. 2, lines 54-56), George et al. does not specifically disclose the isolation of regulatable catalytic DNA molecules. George et al. does not teach the use of a phosphorylated peptide as a peptide effector.

Breaker describes allosterically modified DNAzymes that can be preferably regulated by peptides that are 9 amino acids or less (see Breaker, col. 10, line 4). Additionally, Breaker teaches that the chemical effectors of the allosterically modified DNAzymes may include amino acid derivatives (col. 10).

King describes the various post-translational modifications of proteins that occur in cells. In particular, King (see pages 12-13) teaches that post-translational phosphorylation is one of the most common protein modifications that occur in animal cells. According to King, the vast majority of phosphorylations occur as a mechanism to regulate the biological activity of a protein.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the teachings of George et al. with the teachings of Breaker in the design of the instant invention. One of ordinary skill in the art would have been motivated to make this

modification because George et al. expressly states that their disclosed methods for isolating regulatable polynucleotides can be used to isolate catalytic DNA molecules as well as regulatable ribozymes (col. 2, lines 54-56), and Breaker teaches the isolation of catalytic DNA molecules that are regulated by peptides. Moreover, although George et al. does not teach the use of phosphorylated peptides to regulate the catalytic activity of a DNA polynucleotide, George et al. does teach wherein the effector is provided endogenously, and it is well known in the art that phosphorylation is one of the most common protein modifications that occurs in animal cells (See King, page 12-13). Therefore, absent evidence of unexpected results the endogenous effectors of George et al. encompass phosphorylated peptides.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

12. Claims 1-5, 9-11, 13, and 137 are rejected under 35 U.S.C. 102(e) as being anticipated by Breaker (US 6,630,306).

Breaker describes the isolation of DNA polynucleotides comprising an allosteric site and an enzyme domain spatially distinct from said allosteric site, wherein reversible interaction of a chemical effector with the allosteric site on the DNA polynucleotide reversibly alters the cleavage function or configuration of the DNA polynucleotide (col. 9, lines 18-41). The chemical effectors of Breaker may be amino acids, amino acid derivatives, peptides (including peptide hormones), polypeptides, nucleosides, nucleotides, steroids, sugars or other carbohydrates, pharmaceuticals, and mixtures of any of these. Many are small peptides having 9 or fewer amino acid substitutents and disaccharides and trisaccharides are typical polypeptide and carbohydrate effectors (col. 10). It is noted that the chemical effectors of Breaker include peptides of 9 amino acids or less (col. 10, line 4). In figure 20A, Breaker describes the ability of a histidine cofactor, and a dipeptide containing histidine to catalyze the cleavage activity of a DNAzyme. Figures 18-19 describe the structures of various DNAzymes of Breaker that are allosterically regulated by histidine, note that the DNAzymes are at least partially double and single stranded. The histidine-dependent DNAzymes of Breaker were isolated from a pool of biotin-modified DNAs immobilized on a streptavidin-derivatized column.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Written Description, note that the following rejection contains new arguments with respect to the written description rejection set forth in the Office Action mailed 4-20-04).

Claim 6 recites a DNA polynucleotide that is regulated by a peptide effector comprising: a regulatable, catalytically active polynucleotide having a catalytic domain and a regulatory domain, wherein the catalytic activity of the catalytic domain is regulated by the interaction of the peptide effector with the regulatory domain, and wherein the catalytic activity of the catalytic domain is ligation.

The specification as filed provides a description of the Rev dependent RNA ligase ribozyme, see Example 4, and further describes the in vitro selection and identification of two other examples of polypeptide dependent regulatable, catalytically active nucleic acids, the Cyt18 dependent ribozyme ligase, and the hen egg white lysozyme dependent ribozyme ligase. Furthermore, Applicants provide a schematic diagram of different selection protocols that can be used to identify and isolate peptide dependent RCANAS in Figure 15(c), Figure 17(c), and Figure 23. Figure 22 provides a flow chart of a general method for negative and positive selection of peptide dependent RCANAS. Moreover, the prior art describes the structure of a copper-dependent DNA ligase, see Breaker (1999).

According to the specification as filed the RCANAS of the instant invention are isolated by means of in vitro selection, which involves several components: generation of a random

sequence pool, sieving the random sequence pool for nucleic acid species that bind a given target or catalyze a given reaction, amplification of the sieved species by a combination of reverse transcription, the polymerase chain reaction, and in vitro transcription. Beyond the generation of the random sequence pool, each of these steps can potentially be carried out by a robotic workstation. The pool can be pipetted together with a target molecule. If the target is immobilized on a magnetic bead, then the nucleic acid :target complex can be sieved from solution using an integrated magnetic bead collector. Finally, selected nucleic acid species can be eluted from the complex and amplified via a series of enzymatic steps that include the polymerase chain reaction carried out via an integrated thermal cycler (see page 17, paragraph [0047]).

Apart from the need for further experimentation, neither the prior art nor the specification as filed provides an adequate description of the peptide effector regulated DNA ligase as set forth in instant claim 6. It is clear that in order for the skilled artisan to envision the structure of the peptide regulated DNA ligase of the present invention, the skilled artisan must select polynucleotides from a randomized pool, that function as a DNA ligase, and furthermore test whether or not the DNA ligase is regulated by a peptide effector, the structure of which is also not adequately described. Although the structure for a DNA ligase that is metal-ion dependent is known in the art (see Breaker, 1999), without further experimentation, the skilled artisan would not be able to predict what changes to make to the known DNA ligase structure such that the catalytic activity would then be regulated by interaction with a generic peptide effector. Moreover, apart from further experimentation, the ordinary skilled artisan would not know how to predict the structure of the peptide effector that would function to regulate the activity of DNA

ligases selected from a randomized population of DNA ligase polynucleotides. In the instant case, the specification as filed does not disclose the complete structure of the claimed DNA polynucleotides, which catalyze ligation, or their corresponding peptide effectors. Moreover, there is no clear correlation between the structure of the claimed peptide effectors or their corresponding function, namely to regulate the catalytic activity of a DNA ligase.

According to the MPEP § 2163[R-2]I. "[A]n applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Additionally, see MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed

sequence." In the instant case, the DNA polynucleotides and peptide effectors of the instant invention are clearly isolated only by further experimentation following the teachings of the specification or presently known in the art. Since further experimentation is required, it is concluded that Applicants were not in possession of the full scope of compounds encompassed by the instant claims.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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